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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/250,083	02/15/1999	ANDREA DESSEN	GFN-5341	1676

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EXAMINER

MORAN, MARJORIE A

ART UNIT	PAPER NUMBER
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1631

DATE MAILED: 07/10/2002

Handwritten signature/initials

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/250,083

Applicant(s)

DESSEN ET AL.

Examiner

Marjorie Moran

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 March 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 16, 18 and 20-25 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 16, 18 and 20-25 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 15 February 1999 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☒ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 16, 18, and 20-25 are pending.

Specification

The amendment filed 3/26/02 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows.

The material incorporated by reference from the file "Table 2.txt" from the CD-R created March 22, 2002, as set forth on amended pages 1 and 42, is new matter. The filed labeled "Table 2.txt" and referred to as Table 2 apparently contains structural coordinates for cPLA₂. The originally filed specification did not contain a "Table 2" or structural coordinates for cPLA₂ in any other format; e.g. as a Figure, Addendum or other attachment. No CD-R was filed with or incorporated by reference into the original specification. Applicant states on page 5 of the response filed 3/26/02 that the structural coordinates found in "Table 2.txt" were deposited in the Brookhaven Protein Databank (BPD) as accession number 1CJY and is referred to on page 41 of the amended specification and is incorporated by reference on page 54 of the amended specification. However, page 39 of the *originally filed* specification states that "Coordinates *will be* deposited at the Brookhaven Protein Databank" (emphasis added by examiner) and does not incorporate crystal coordinates (or Table 2) by reference anywhere. The PDB record (accession number 1CJY) indicates that crystal coordinates

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were deposited on April 20, 1999, which is AFTER the filing date of the instant application. The article cited by the PDB was issued by Cell (IDS ref. Dessen et al. Cell. vol. 39, pp. 349-360) on April 30, 1999, again AFTER the filing date of the instant application. As the crystal coordinates were not deposited or otherwise made publicly available until AFTER the filing date of the instant application, it is unlikely that the crystal coordinates contained in Table 2 were incorporated by reference from either the PDB or another publication in the originally filed specification. The originally filed specification did not disclose crystal coordinates corresponding to Table 2 anywhere. The originally filed claims did not recite the crystal coordinates of Table 2. As the information contained in "Table 2.txt", incorporated by reference from a CD-R created March 22, 2002, is not supported by either the originally filed specification or claims, the substitute specification filed 3/26/02 contains new matter and is objected to.

Applicant is required to cancel all new matter in reply to this office action.

Further added material which is not supported by the original disclosure is as follows.

The newly amended specification refers to SEQ ID NO's 2 and 3. The amendment of 7/27/00 added new pages 53-56 which were the paper sequence listing identifying SEQ ID NO's 1 and 2. SEQ ID NO: 2 was disclosed in the originally filed specification on page 4, and thus was not new matter. The entirety of SEQ ID NO: 1 was not specifically disclosed by the originally filed specification; however, the originally filed specification taught on page 6, lines 1-5, a cPLA₂ sequence found in Table 1 of US

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Patent 5,527,698. The specification was amended to state that the cPLA₂ sequence was found in SEQ ID NO: 1 and in Table 1 of US Patent 5,527,698. As the amended specification disclosed that the sequence in Table 1 of US Patent 5,527,698 is the same as SEQ ID NO: 1, SEQ ID NO: 1 is not considered new matter. Applicant is advised that if SEQ ID NO: 1 of the sequence listing is not identical to that taught in Table 1 of US Patent 5,527,698, then SEQ ID NO: 1 is considered new matter. Neither the originally filed specification nor the sequence listing teach a SEQ ID NO: 3 or identify a sequence corresponding to a SEQ ID NO: 3.

The pentapeptide which corresponds to SEQ ID NO: 2 of the sequence listing is now labeled SEQ ID NO: 3 on page 4 of the substitute specification filed 3/26/02, and the polypeptide sequence labeled SEQ ID NO: 1 of the sequence listing now appears to be labeled as SEQ ID NO: 2 throughout the newly amended specification. The examiner has not been able to find a sequence labeled "SEQ ID NO: 1" in the amended specification. If applicant intends to disclose SEQ ID NO's 2 and 3, then the new sequence (SEQ ID NO: 1?) is new matter. Further, if there are three sequences, then the specification fails to comply with the sequence rules. Applicant is reminded that sequence numbers must start at 1 and be sequential (i.e. there must be a SEQ ID NO: 1). Applicant is further reminded that sequences must be listed in the sequence listing AND in a CRF, and that the sequence listing and CRF must be identical. The instant sequence listing and CRF contain only SEQ ID NO's 1 and 2. The substitute specification filed 3/26/02 does not contain sequence listing pages, but does contain "substitute" pages numbered through p. 55. As applicant has not specifically deleted

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the sequence listing pages, it is assumed that the prior sequence listing pages (pp. 53-56, as filed 7/27/00) are not amended or deleted, and the sequence listing page numbers will be changed to pp. 56-59, respectively.

It is possible that the "new" SEQ ID NO's are merely a typographical error. If so, this objection may be overcome by amending the specification to disclose the correct SEQ ID NO's (i.e. SEQ ID NO's 1 and 2). Applicant is reminded that the substitute specification filed 9/5/00, which included substitute sequence listing pages, was not entered.

Applicant is required to cancel all new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

In view of the amendment to the specification (Table 2), which discloses crystallographic coordinates for cPLA₂, the rejection of claims 16, 18, and 20-25 under 35 USC 112, first paragraph, with regard to enablement due to lack a pure and/or crystallized molecule, is hereby withdrawn. Applicant is advised, however, that Table 2 is considered new matter, as set forth above; cancellation of Table 2 may result in reinstatement of the enablement rejection.

Claims 20, 22, 23 and 25 are again rejected, as previously set forth in the office action of 10/22/01, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

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Applicant has not set forth any arguments with regard to lack of a teaching for how to synthesize putative inhibitors or with regard to lack of a teaching for how to determine atoms or amino acids involved in catalysis; nor has an amendment been filed which overcomes the rejection, therefore the rejection of claims 20, 22, 23, and 25 is maintained.

Claim 18 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an ENABLEMENT rejection.

Claim 18 recites a step of determining the interaction between a candidate substance and a model of the structure of cPLA₂. A model, according to Merriam-Webster's dictionary, is an imitation or emulation; i.e. a model is not the thing itself. The specification does not disclose how to determine the interaction of an emulation of the structure of cPLA₂ with a candidate substance. In the instant case, based on the teachings of the specification, the examiner interprets a "model of the structure of cPLA₂" to be a computer representation (3D emulation of crystal coordinates or data set representing a spatial arrangement of atoms). A "substance" is interpreted to be an actual compound, not a data set or 3D computer emulation. Neither the specification nor the prior art teach how to determine the interaction between an actual, physical substance or compound and a virtual (computer generated) structure or model of a structure of an enzyme, therefore claim 18 is not enabled.

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Claims 23 and 25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a LACK OF WRITTEN DESCRIPTION rejection.

Neither an electrostatic patch region nor ANY region comprising amino acids Arg467, Arg485, Lys488, Lys544, and/or Lys543 is described by the instant specification. Parent claim 23 recites formation of non-covalent bonds with amino acids in an electrostatic patch region of cPLA₂. Claim 25 limits the amino acids in the electrostatic patch region to be Arg467, Arg485, Lys488, Lys544, or Lys543. The amended specification discloses on page 15, lines 4-16, a highly basic region which would be expected of a region making multiple electrostatic contacts. The specification also discloses on page 15, lines 9-11 that it is "impossible to accurately define the true size of the basic patch." The specification further discloses on page 18 that the highly basic region is *hypothesized* as making electrostatic contacts. The basic patch of pages 15 and 18 is not disclosed as one which is KNOWN to be an electrostatic region. Yet further, the basic patch disclosed on pages 15 and 18 is not specifically defined by the specification. That is, the patch is discussed in "regional" terms on page 15, but the area or length of the patch is not disclosed anywhere, and in fact, the specification discloses on page 15 that the true size of the patch is impossible to determine. Thus, the specification fails to specifically disclose an electrostatic patch region in cPLA₂. The specification does not disclose that the basic patch or any other region comprises

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Arg467, Arg485, Lys488, Lys544, and/or Lys543. Figure 2C discloses Arg 57 and Arg59, but these do not appear to be in the region hypothesized to be the "basic patch". None of the Figures discloses the residues recited in claim 25. The specification does not teach these residues to be part of any specific region or patch, etc. of cPLA₂. The specification fails to describe an electrostatic patch region, and fails to describe one comprising Arg467, Arg485, Lys488, Lys544, and/or Lys543, therefore the claims are rejected for lack of written description.

Claims 16, 18, and 20-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 recites a method wherein the interaction of a candidate species with a model/data set embodying the structure of cPLA₂ is studied (step (b)). Although neither the claim nor the specification specifically recites or discloses that the "species" is a *data set* representing a compound, the claim is interpreted as if it recited study of an interaction between data sets. However, in view of this interpretation, it is unclear whether applicant intends the species of step (c) to also be a data set, or to be an actual compound, therefore the claim is indefinite. It is noted that the candidate "species" can not represent BOTH a data set and an actual compound, as an actual compound can not interact with a data set; nor can a data set BE an agonist or antagonist of enzyme activity or binding. Applicant is reminded that any amendments to the claims must be fully supported by the originally filed specification and/or claims.

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Claim 16 recites a method wherein the interaction of a candidate species with a model/data set embodying the structure of cPLA₂ is studied, but does not set forth any specific method steps for “studying” the interaction. As set forth above, the claim is interpreted as if it recited “study” of the interaction between data sets. However, a “study” of interaction between data sets can be performed in a variety of ways: docking or fitting between three-dimensional (3D) representations of the entire enzyme and the candidate species; docking between parts or subunits of a 3D model of the enzyme and the entirety of the candidate species, docking between parts or subunits of the entirety of a 3D model of the enzyme and parts or subunits of a 3D model of the candidate species, mathematical “fitting” or aligning atoms of the enzyme with atoms of the candidate species to find those configurations with lowest energy, or lowest torsional strain, or some combination thereof (i.e. using algorithms but not a 3D model), etc. As many ways of “studying” an interaction between data sets representing an enzyme and possible ligand (e.g. agonist or antagonist) are generally known in the art, the claim is enabled. However, as neither the specification nor claims set forth any particular method steps for “studying” the interaction, it is unclear what method steps applicant intends, and one skilled in the art would not know the metes and bounds of the claim, therefore the claim is indefinite.

Claim 16 recites a method wherein an interaction of a candidate species with an enzyme is studied, then a species is selected which is predicted to act as an agonist or antagonist. The claim fails to recite any criteria for predicting agonist or antagonist properties or activity in a candidate species, or any method steps for identifying an

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agonist or antagonist of cPLA₂, therefore the claim is indefinite. It is noted that a compound may be identified as one which binds to a enzyme, and may even be identified as one which binds to a known "active site", but may not necessarily be one which acts as an agonist or antagonist (i.e. not all compounds which bind to an enzyme affect the activity thereof). For support, see KRAMER et al. (EP0501779), pp. 4-5. In addition, agonists and antagonists, by definition, affect an enzyme in opposite ways. Method steps or criteria for predicting an agonist do not necessarily also predict an antagonist, and vice versa. As it is unclear what criteria or method steps are intended by applicant for predicting a species which is an agonist or antagonist, the claim is indefinite.

Claim 18 recites a process of identifying a substance that inhibits cPLA₂ activity or membrane binding comprising determining the interaction between a model of the structure of cPLA₂ and a candidate substance. Claim 18 does not recite any method steps for "determining the interaction" between the structure model and a candidate substance. Many computer methods are known for determining an interaction between models of an enzyme and a compound, as set forth above. In addition, many methods are known in the art for determining the interaction between an enzyme and a candidate ligand. As it is unclear what steps applicant intends to determine the interaction between a model of the structure of cPLA₂ and a candidate substance, one skilled in the art would not know the metes and bounds of the invention, and the claim is indefinite.

Claim 18 recites a "process of identifying" an inhibitor in lines 1-2, but fails to recite any step specifically identifying an inhibitor. The only steps recited in one of determining an interaction; not all compounds which "interact" with the enzyme are necessarily inhibitors, therefore this is not a step of identifying of an inhibitor. As it is unclear whether the method actually identifies an inhibitor, the claim is indefinite.

Claim 20 recites the phrase "the crystal structure co-ordinates of cPLA₂" in lines 4-5. There is no antecedent basis for this term in the claims, therefore the claim is indefinite.

Claim 20 recites a step (c) of "determining whether the potential inhibitor inhibits the activity of cPLA₂". Claim 20 does not recite any specific steps for carrying out the determination of step (c). Many methods are known in the art for "determining" if a compound is an inhibitor of a particular activity, therefore the claim is enabled. However, as it is unclear what method steps applicant intends for his "determination", and it is unclear what "activity" is to be inhibited (e.g. lipid binding only, transmembrane movement, catalysis, etc.), one skilled in the art would not know the metes and bounds of applicant's inventive method, and the claim is indefinite.

Claims 21 and 24 each recite a crystal of "space group P2₁P2₁2" wherein "a", "b", and "c" are limited to a specified length. Neither the specification nor claims define a "space group P2₁P2₁2" nor what bonds are considered "a", "b", and "c". The specification discloses a "space group P2₁P2₁2" in several places, but nowhere discloses the atoms or region or crystal coordinates of cPLA₂ which are designated space group P2₁P2₁2. The Figures show several space-filling models of cPLA₂ and

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define various atoms in specified positions, but do not defined a space group $P2_1P2_12$ anywhere. As it is unclear what portion of $cPLA_2$ is intended to be space group $P2_1P2_12$, claims 21 and 24 are indefinite.

Claim 23 recites a step (c) of "determining whether the potential inhibitor inhibits the membrane binding of $cPLA_2$ ". Claim 23 does not recite any specific steps for carrying out the determination of step (c). Many methods are known in the art for "determining" if a compound is an inhibitor of a particular activity, therefore the claim is enabled. However, as it is unclear what method steps applicant intends for his "determination", one skilled in the art would not know the metes and bounds of applicant's inventive method, and the claim is indefinite.

Claim 23 recites " $cPLA_2$ electrostatic patch region" in line 4. There is no antecedent basis for this term in the claims, therefore the claim is indefinite. In addition, a " $cPLA_2$ electrostatic patch region" is not described or defined by the specification or in the claims, as set forth above. It is not disclosed that the electrostatic patch is the same as the basic patch, and even if it were, the basic patch is not defined such that one skilled in the art would know what atoms or coordinates are included in the basic patch. For these reasons, claim 23 is indefinite.

Conclusion

No claims are allowed.

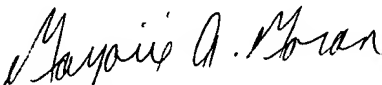
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marjorie A. Moran whose telephone number is (703)

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305-2363. The examiner can normally be reached on Monday to Friday, 7:30 am to 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (703) 308-4028. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 872-9306 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to a patent analyst, Tina Plunkett, whose telephone number is (703) 305-3524.


Marjorie A. Moran
Examiner
Art Unit 1631

July 9, 2002

Attachment for PTO-948 (Rev. 03/01, or earlier)
6/18/01

The below text replaces the pre-printed text under the heading, "Information on How to Effect Drawing Changes," on the back of the PTO-948 (Rev. 03/01, or earlier) form.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the Notice of Allowability. Extensions of time may **NOT** be obtained under the provisions of 37 CFR 1.136(a) or (b) for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit the drawing corrections within the time period set in the attached Office communication. See 37 CFR 1.85(a).

Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.